Exhibit D

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A NOVEL COMPOSITE SLING FOR THE TREATMENT OF STRESS URINARY INCONTINENCE: FIRST CLINICAL EXPERIENCE

JEFFREY BLITSTEIN, M.D., RICHARD CHANG, M.D., ARNALDO F. TRABUCCO, M.D., F.A.C.S.

Departments of Urology, SUNY Downstate Medical School, Brooklyn, NY Department of Urology, Saint Vincent Catholic Medical Centers - Brooklyn and Queens, St Johns Queens Hospital Division, Elmhurst, NY

ABSTRACT

Objectives: The purpose of this study was to design a mesh to improve the procedure for the surgical correction of stress urinary incontinence (SUI) using a new surgical synthetic composite sling. The sling was designed to prevent the inherent complications of chronic retention and urethral erosion, associated with traditional synthetic polypropylene slings and to provide the urologic surgeon with a minimally invasive user-friendly approach.

Methods: Thirty patients with urethral hypermobility SUI were treated with this sling. The sling, composed of both absorbable and non-absorbable components, is implanted using a modified Stamey approach. Follow-up was performed retrospectively. Follow-up was for 14-54 months, with a mean 30.2 months.

Results: All patients (30 patients, 100%) operated on had cure of incontinence. Irritative voiding symptoms improved in all patients. No morbidity or complications were seen.

Conclusion: The preliminary results indicate that this approach is safe, effective, and well tolerated compared to other available surgical materials and techniques. This procedure is, minimally invasive, easily reproducible, and can be performed as a short-stay surgical procedure using materials that are found in any operating room.

Key Words: Incontinence, Sling, Mesh, Tension free sling, Pubovaginal sling, Polypropylene, Urethropexy, Needle suspension, T-Sling, Stress urinary incontinence.

INTRODUCTION

We face continuing challenges for the optimal form of treatment for stress urinary incontinence (SUI). Long-term outcome studies have revealed disappointing results for percutaneous needle suspensions and other sling substitutes secondary to failure due to the recurrence of urethral hypermobility or creation of urethral obstruction [1].

The pubovaginal sling procedure is an established, reliable technique for correcting Type 3 (intrinsic sphincter deficiency, ISD) SUI, and Type 2 SUI with coexisting ISD [2]. Recently, the pubovaginal sling procedure has been popularized and used as a primary modality to treat all forms of SUI including urethral hypermobility (type 1 & 2) in the female patient [3].

It is estimated that 30-65% of women with SUI present with mixed incontinence [4]. Theoretically, preoperative irritative voiding symptoms (IVS) can also be corrected when the appropriate tension is applied to the sub-urethral sling relieving the traction on the pelvic nerves innervating the bladder [5].

Weakness of the urethropelvic ligament (UPL) (endocervical and periurethral fascia) with its attachments to the arcus tendinous and urethra correlates with urethral hypermobility and SUI. This anatomical defect is a herniation of the pelvic contents. Anatomical corrective surgery has addressed these issues in the past with sub-optimal long-term results without the use of autologous or prosthetic sling material [2, 6-9]. Many procedures have been utilized in order to attempt to re-support the UPL. If one were to reconstruct the fascia, one could potentially correct all forms of SUI secondary to urethral hypermobility.

Complications of urethral sling procedures using a synthetic prosthesis have been reported: urethral obstruction, urinary retention, mesh erosion, extrusion, infection and nerve entrapment [10-11].

A novel sling was designed to eliminate these inherent complications. The main objective of this operation is to address all anatomical concerns using a modified Stamey approach. It is also designed to prevent the inherent complications seen with prosthetic material positioned underneath the urethra and bladder neck.

MATERIALS AND METHODS

Surgical Material: The Tension-Free Sling (T-Sling) is a mesh composed of two different materials. The lateral aspects of the mesh are composed of a 2cm width monofilament polypropylene (PP) mesh with a 1cm absorbable monofilament of polydioxanone (PDO). The sling length in this study was tapered by hand for each patient intraoperatively by measuring the distance between the arcus tendinous.

PATIENT EVALUATION

A total of thirty female patients who underwent this surgical procedure were retrospectively studied. All patients had been educated preoperatively as to the potential risks and complications including potential (early or late) failure prior to the operation. All patients that chose to undergo this procedure had consented preoperatively and reported herein (Table 1).

Table 1: Preoperative patient data treated with T-Sling

No. pts. with SUI	30
Mean duration of symptoms prior to surgery (1-15yrs)	6.1yr
Mean patient age (35-78years)	59.25yr
No. pts. with Irritative voiding symptoms (urgency and frequency)	12
No. pts. with Atrophic Vaginitis	12
No. pts. Total Abdominal Hysterectomy + Bilateral Oophorectomy	4
No. prior Total Abdominal Hysterectomy	2
No. prior Vaginal Hysterectomy	8
No. Parity by vaginal delivery (25), Caesarian Section (2)	27
No. pts. with family history of stress urinary incontinence	8
No. pts. with prior SUI procedures (Kelly 15, Vesica 1, Gittes 2, Pereyra 1, Stamey 2)	17
No. pts. post menopause	14
No. pts. with uterine prolapse	1
No. pts. with cystocele (grade I 1,II 2,III 14, IV 3)	20
No. pts. with enterocele	8

All patients elected for the T-Sling procedure were confirmed to have stress Type 1, Type 2 - SUI diagnosed by complete history and physical examination, and cotton swab test. Patients with ISD (Type 3), with or without a cystocele component were not tested prior to surgery due to the obvious nature of the urethral hypermobility. Valsalva leak point pressure was not routinely measured on all patients and thus is not available for analysis. All patients had a urinary questionnaire, 24-hour voiding diary, pad test, post void residual volumes (before and after surgery). Pre-op evaluation also included urinalysis, cotton swab test,

Marshall test, uroflow evaluation, cystoscopy, IVP, urodynamics and vaginoscopy. Evaluation of patients was determined by diapers, voiding diaries and objective demonstration on physical examination. All patients treated had a negative impact of their incontinence upon their lifestyle. A standard questionnaire was used for follow up (see appendix) [12]. IVS (frequency and urgency) were determined by subjective evaluation and voiding diary. Postoperative evaluation was conducted one week, one month, three months and every six months.

Post menopause patients were treated with Estrogen cream for a minimum of 3 months preoperatively to augment the vaginal mucosa with co-existing atrophic vaginitis. Preoperative antibiotics were administered to all patients.

SURGICAL PROCEDURE

The T-Sling procedure consists of two surgically implanted meshes connected by a Polybutester suture as a modified Stamey approach with the use of a supporting synthetic composite mesh sling. The vaginal mucosa is incised (3-4cm) longitudinally at the level of the bladder neck. Sharp dissection is performed to expose the inferior surface of the urethra and lateral pelvic sidewalls. Blunt finger dissection is used to develop the existing plane inferior to the endopelvic fascia, confirming the deficiency of the structural integrity of the UPL up to the arcus tendinous.

If a concomitant cystocele is present, this is repaired first. The T-Sling is trimmed to 2cm more than the distance between the arcus tendinous so that it can be placed under the UPL in a tension-free fashion from one arcus tendinous to the other.

A single 1-2cm suprapubic incision is made. Sharp dissection is performed from the fibro-fatty tissue down to the anterior rectus fascia at the level of the linea alba insertion to the pubic bone. A spinal needle is used to inject 100cc sterile water in the space of Retzius allowing the fluid to dissect a plane between the pubic bone and bladder. A Stamey needle is passed behind the pubic bone after penetrating the anterior rectus fascia at its inferior insertion near the pubic bone. The needle is first passed para-urethral and is then positioned medial to the arcus tendinous and passed into the vaginal incision. One pass is utilized for this maneuver.

A 0 – Polybutester suture is laced 1cm medial to the ends of the PP mesh. The sutures are then introduced into the eye of the Stamey needle and are then drawn upward. The center of the T-Sling is aligned under the urethra to lie flat on either side from one arcus tendinous to the other with flat apposition underneath the destroyed or deficient UPL. Both sutures are delivered through the same puncture site to prevent any potential for nerve entrapment. Cystoscopy is then performed to assess for a bladder perforation and the urinary bladder is filled with fluid.

At the termination of the procedure, the second smaller (1cm) PP mesh is then placed in the anterior suprapubic incision with the sutures placed through the holes of the mesh on both sides. The mesh is then placed to lie flat over the linea alba. Both sides are performed in an identical fashion. Excess vaginal mucosa due to a concomitant cystocele is trimmed. The vaginal mucosa is then closed with a running continuous interlocking stitch with 2-0 absorbable sutures before tying the sutures.

Before tying the suprapubic sutures a provoked Valsalva cough test while under spinal or epidural anesthesia is performed. The surgeon then determines the “minimal” assessment of tension on tying the sutures to maintain continence. Alternatively, if the patient is under general anesthesia, the sutures are tied with a cotton swab in the urethra allowing for an approximate 15-degree deflection upward by tying the sutures under minimal tension.

The suprapubic incision is closed with 4-0 absorbable suture and Steri strips applied. Vaginal packing coated with Neosporin® ointment is placed for 12 hours. A Foley catheter is inserted to leg bag urinary drainage for 3-7 days.

RESULTS

All terms and definitions used in this study were in accordance with the International Continence Society [14]. All patients had successful outcomes as measured by the lack of SUI with a 100% success ranging from 14-54 months follow-up **(Table 2).** Patients’ satisfaction was addressed by subjective (modified Urogenital Distress Inventory form) and objective evaluation (see appendix) [12]. Cure was defined as no loss of urine due to stress or urge incontinence, objectively by 24-hour diary and pad test, and subjectively by the patient feeling cured. Failure was defined as poor objective results with the subjective feelings by the patient that the surgery had failed, but none was reported. Improvement was defined as a good, fair and poor by subjective and objective evaluation [13]. Ten of the twelve patients with preoperative IVS symptoms had resolution of their symptoms 1-8 months with one improvement prior to the development of adult onset diabetes mellitus.

Table 2: Postoperative evaluations with T-Sling

No. pts. Cystocele repair	17
No. pts. enterocele repair	8
No. pts. Vaginal hysterectomy	1
Complications (intra-operative /post-operative)	0
Mean hospital stay (20-48hrs)	24hrs
Mean follow-up interval (14-54months)	30.2mo
No. pts. Satisfied with surgical results	30
No. pts. Cured (dry) of incontinence	30
No. pts. persistent irritative voiding symptoms	2
No. pts. receiving regional anesthesia	29
No. pts. receiving general anesthesia	1
No. pts. with pain after seven days	0
No. pts. with de-novo Irritative Voiding Symptoms	0

The operating time of the procedure was approximately 30 minutes for each patient. This was calculated after surgical repair of the cystocele. Estimated intra-operative blood loss was 200-400 cc. Epidural or spinal anesthesia was performed on 29 patients. One patient undergoing a concomitant vaginal hysterectomy was placed under general anesthesia.

All patients were seen in the office for evaluation of post void residual, pain, diary, pad test and physical examination at one week, one month, three months and every six months with follow-up for 14-54 months. All patients voided spontaneously and no new onset urge incontinence was noted.

Partial retention occurred in one patient, post void residual volume 300 cc, with a concomitant hysterectomy, which resolved with a Foley catheter insertion for a total period of two weeks. This patient had preoperative retention with 900cc post void urinary volume. Average hospital stay was 20-24 hours. No patient complained of pain on the seven-day postoperative visit or subsequent visits. All patients stated that their lifestyles had improved dramatically.

DISCUSSION

In patients with pelvic prolapse the defective regenerative fibroblastic foundation in these patients may not be adequate to establish a sufficient connective tissue fascial support structure. Reports have documented an “increased” collagenase, elastase activity, type III collagen synthesis, and fibroblast generation interval, leading to an overall decreased fascial support structure inherent (possibly genetic) in this population [15-16].

Many types of allogenic, xenogeneic and synthetic materials have been used in an effort to provide readily available and reliable sling material without the additional morbidity and operative time associated with fascia harvesting. Synthetic materials are easy to store, readily available and avoid the harvesting procedure of an autograft.

Designing the ideal synthetic material to replace autogenous fascia continues to be a challenge. The synthetic material should provide a non-antigenic framework that is gradually interlaced or replaced by host fibroplasia resulting in a strong stable aponeurotic structure [17].

Many synthetic biomaterials have failed clinical trials. Some major problems have been pain, fragmentation, extrusion, erosions, early loss of tensile strength, shrinkage and low tolerance to infections.

Polypropylene has become the most commonly used biomaterial for the repair of abdominal wall hernias by general surgeons. This provides a durable framework for the in-growth of collagen and has a high tolerance to infection. Reports of large numbers of patients (inguinal hernia surgery) with long-term follow-up results have been excellent. However, its use in the lower urinary tract can create complications when improperly placed. Polypropylene can be safely used in the treatment of SUI [18].

When placed into the body a fibroblastic reaction is produced that is immediate and allows the material to remain in place. Numerous reports have also indicated 20-30% shrinkage in length and pore size of Marlex mesh (flat) within a twelve-month interval [19-20]. A mesh placed in a 3 dimensional shape may shrink up to 75-80%. Due to the weave, pore size and consistency, an increased shrinkage rate for prolene and other flat PP weaves is postulated where comparative studies are presently lacking [21-22].

Using less quantities of mesh, not more, reduces the possibility of complications. We believe it is not the mesh, per se, that causes complications or recurrences after implantation. Its how, why, how much and where the prosthetic material is implanted under the urinary tract that may cause complications during its shrinkage period. Overall, non-absorbable meshes should not be placed against any abdominal or pelvic visceral organ including the bladder or urethra if possible.

Polypropylene is best used in a tension-free fashion with flat apposition to the tissue. Any form of tension or movement on tissues will impede proper tissue healing with normal collagen fibril ingrowth and healing.

Many new variations of the PP have been made which do not address issues such as obstruction, erosion and shrinkage [23-25].

In theory, when PP mesh is used as a continuous sling for SUI, any Valsalva maneuver will induce intermittent hydrostatic pressure from the abdominal-pelvic contents onto this non-movable, non-expanding material. The mesh will also tend to curl acting as a non-expandable rigid circular bridge. Over time, a mesh will shrink contributing to an increase in pressure on the urethra or contiguous organs. This can translate into an increased resistance during the shrinkage of the mesh. Previous reports of retention and urethral erosion have been documented with the use of PP when used directly under the urethra [26]. This continuous pressure eventually translates into an erosive process. Eventual migration of the mesh material will penetrate the urethra or even bladder neck or possibly result in urinary retention [27]. This may be more prevalent in obese and COPD patients. Complications of retention and urethral erosion may require a secondary surgical (urethrolysis) procedure [28].

Any excess tension on the sling may lead to irritative and obstructive voiding symptoms and urinary retention. Possibly the sub-trigonal elevation relieves the tension on the pelvic nerves innervating the trigone and the supporting sling allows for a tension-free support postoperatively. This many contribute to de-novo IVS if there is escalating tension under the bladder neck support structures.

Surgically implanting PP away from the urethra in a tension-free fashion may preserve the urethral vascular supply and mucosal seal. By incorporating absorbable material into the design of the sling we have now introduced a preventive measure of escalating tension under the urethra. Once dissolved this provides a ‘tension-free suspension sling’ (T-Sling) around the urethra and supporting fascia while simultaneously avoiding any possible erosion.

The design of the T-Sling addresses these issues by the introduction of two types of material. The unique property of the T-Sling is the central PDO portion of the prosthesis, which was designed to allow the central area to be absorbable. Assuming if 100 days are necessary for complete healing to occur postoperatively, one can understand the design of this sling. After 100 days, the central portion is dissolved by hydrolysis. The two non-absorbable portions are detached from themselves rendering a true ‘tension-free sling’ under the urinary tract. Any undue tension that may subsequently develop sub-urethrally due to shrinkage of the mesh is eliminated after 3 months postoperatively. Increased tension over time is prevalent with other surgical prosthesis when one uses a continuous conventional non-absorbable mesh due to shrinkage [29-30].

The fibrosis reaction created by the two ends of PP allows for reconstituting the support of the periurethral fascia when placed from one arcus tendinous to the other. This now rebuilds the primary anatomical preoperative defect (UPL) by secondary intention.

Infection is reduced due to the inert properties of monofilament PP. Use of one puncture site on either side of the lower abdominal suprapubic area and virtually eliminates any possibility of nerve entrapment and postoperative pain.

CONCLUSION

This report describes the use of a novel composite sling designed to reduce the complications seen with other synthetic slings. With the problems of chronic retention and urethral erosion associated with surgical synthetic prosthesis procedures for SUI, the T-Sling could potentially eliminate intrinsic concerns and complications. The procedure is minimally invasive and results in a short hospital stay.

The surgical procedure is technically simple and easily reproducible. The universal simplicity of this operation, when treating SUI, can be added to discretion of the surgeon’s surgical armamentarium.

This is the first study of the T-Sling, with 30 patients with a maximum follow-up of 54 months. There is no magic bullet for surgical treatment of SUI. The potential use in Type 3 SUI (ISD) needs to be evaluated separately in a prospective manner. Long-term studies of this procedure need to be conducted with large numbers in a prospective, randomized, controlled fashion to validate the promising findings of this novel surgical composite sling.

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